

# Pharmacogenetics: the ethical issues

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The Nuffield Council on Bioethics has issued a consultation on ethical issues raised by developments in pharmacogenetics. The potential of using pharmacogenetic information to improve the efficacy and safety of prescribing medicines is clear. Some have even made the optimistic claim that personalised medicine — ‘the right medicine, for the right patient, at the right dose’ — will only be a matter of time. However, both research in pharmacogenetics and its applications raise ethical, legal, social and regulatory issues which is important to consider now.

Issues in pharmacogenetics that need to be addressed include the implications for the cost and availability of medicines, the use and storage of genetic information obtained for pharmacogenetic analysis, and the possible stratification of patient groups on the basis of genetic information. The Nuffield Council has established a Working Party to consider these issues (see Box 1). As part of its deliberations, the Working Party is holding a consultation with the public. Interested individuals and organisations are invited to contribute their views about the implications of pharmacogenetics for the pharmaceutical industry, providers of healthcare and individual patients.

The consultation document poses a number of questions, based on three main themes: the development and regulation of medicines, the provision of tests and medicines and

the use and storage of genetic information.

## THE DEVELOPMENT AND REGULATION OF NEW MEDICINES

What might be the effect of findings in pharmacogenetics on the development of new medicines? According to a study by the Boston Consulting Group, the cost of developing a new medicine could be reduced dramatically using pharmacogenetics, to about 60% of the \$880 million usually required to develop a medicine.<sup>1</sup> Pharmacogenetic information could have an impact on both the cost and conduct of clinical trials. The use of genetic information could ensure that only those patients most likely to benefit from a medicine would be enrolled in a trial. This approach would help to protect participants by excluding those who would be unsuitable recipients, either because they are less likely to respond or because they are at risk of adverse reactions. It could also make research more efficient. Fewer participants might be needed, which could result in reduced costs and quicker completion of the processes required to bring a medicine to market. The question therefore arises as to whether pharmacogenetic testing of participants in trials should become a regulatory requirement for the development of all medicines in future.

The application of pharmacogenetics could also lead to an increasing range of specialised medicines, with smaller, more narrowly defined groups of patients for whom the medicine is appropriate. This is likely to have an impact on the current emphasis on so-

called ‘blockbuster’ medicines. It has often been suggested that the pharmaceutical industry will be unlikely to develop medicines for very small groups of patients, because of the balance of economic costs and benefits involved. Currently, some medicines that treat rare diseases are called ‘orphan medicines’ because they are unlikely to generate sufficient economic revenue to the pharmaceutical industry. The research and development of such medicines may be promoted by providing legal and financial incentives through specific regulation. Examples include the 1982 US Orphan Drug Act, and in Europe, the Regulation on Orphan Medicinal Products, established in 2000. Pharmacogenetics may extend the volume of orphan medicines, by stratification of the patient population into subgroups. Will progress in pharmacogenetics bring about the need for additional regulatory measures to encourage the development of clinically desirable but economically unprofitable medicines?

## THE PROVISIONS OF TESTS AND MEDICINES

Considering both new and existing medicines, might the applications of pharmacogenetics exacerbate inequalities in the provision of healthcare? The providers and funders of healthcare face considerable challenges. Cost-effectiveness is increasingly important when considering treatments and therapies in the face of limited budgets. There are questions about how predictions of efficacy and safety, as well as cost, should be integrated in decision-making concerning the provision of particular treatments to patients in both public and private healthcare systems.

A further question concerns where the responsibility should lie for providing a pharmacogenetic test. For individual therapy, should tests be available directly to patients over the counter or on the Internet, or should they only be available through general

**Box 1 Nuffield Council on Bioethics**

The Nuffield Council on Bioethics is an independent body, established in 1991 to identify, examine and report on the ethical questions raised by recent advances in biological and medical research. The Council provides advice that assists policy-making, addresses public concerns and stimulates debate.

Previous publications include:

- Genetics and human behaviour: the ethical context (October 2002)
- The ethics of patenting DNA—a discussion paper (July 2002)
- The ethics of research related to healthcare in developing countries (April 2002)
- Stem cell therapy: the ethical issues (April 2000)
- Genetically modified crops: the ethical and social issues (May 1999)
- Mental disorders and genetics: the ethical context (September 1998)
- Animal-to-human transplants: the ethics of xenotransplantation (March 1996)
- Human Tissue: ethical and legal issues (April 1995)
- Genetic screening: ethical issues (December 1993)

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**THE USE AND STORAGE OF GENETIC INFORMATION**

New pharmacogenetic tests will require the large-scale use and storage of genetic information, raising issues about consent to testing, questions of privacy and access to genetic data. Many of these issues are familiar from broader debates about genetic testing and the use personal genetic information.<sup>3</sup> However, it is important to consider whether these discussions can be applied in the particular case of pharmacogenetic testing, both during clinical trials and in primary care.

**Confidentiality, Consent and Feedback in Clinical Trials**

With regard to clinical trials, questions about confidentiality and consent are likely to be raised. Pharmaceutical companies and other researchers often collect and store genetic samples from participants in clinical research. Companies may store such information in order to replicate or dispute findings that other researchers might present at a later date. These samples might also be used for further testing. Is the storage of genetic information for the purpose of pharmacogenetic analysis categorically distinct from storage of other kinds of genetic information, for example information about susceptibility to disease? What kinds of consent should be required for the collection of samples?

There are also questions about feedback that is given to participants during clinical trials. Should researchers provide individual feedback about genetic information obtained from participants during research in pharmacogenetics? This would only be possible if the samples are stored in such a way as to be linked to particular participants. Careful consideration will therefore need to be given to the level of anonymity that should be applied to genetic information stored as part of research.

Countries vary in their regulations on the protection of personal data. In some countries regulations allow patients access to all medical information, including genetic information, and require that participants in research receive individual feedback.

practitioners (GPs) as part of a decision about the use of a prescribed medicine? In the UK, the Human Genetics Commission (HGC) has recently been asked by the Government to give advice on the supply of genetic tests direct to the public. The consultation document raised the issue of pharmacogenetic test. It is expected that an opinion will be produced in early 2003 and the HGC may make recommendations which have implications for pharmacogenetics.

It is also unclear how public and private providers of healthcare will react to the expectations of patients. Conflict could arise when genetic tests are used as the basis of a GP's decision as to whether a patient qualifies for a particular treatment. In many cases, the result of a genetic test will not reveal a simple status of either 'responder' or 'nonresponder' to a particular medicine. Rather, tests will reveal the likelihood of response. Should a patient who has only a 20% likelihood of responding to particular treatment receive it through the public healthcare system? What about a 50% likelihood?

**RACE AND ETHNICITY**

There is a possibility that pharmacogenetic information will vary according to racial or ethnic origin. For example, variation in the gene for the enzyme CYP2D6 is known to differ between different racial groups. This enzyme metabolises a large number of medicines. Of the Caucasian population, 7% have a genetic variant that results in markedly reduced activity of

the enzyme and this group is therefore poor metaboliser of many medicines. Among Ethiopian and Saudi Arabian populations however, there is a high frequency of a genetic variant that results in markedly increased activity of the CYP2D6 enzyme.<sup>2</sup>

The use of concepts such as race and ethnicity in the context of pharmacogenetics is contentious. There is considerable genetic variation both within and between racial groups, and it is not clear whether attempts to categorise people in this way can be justified on scientific grounds. However, what might be the implications of finding a genetic variant that influences the response to a medicine in a particular racial or ethnic group?

One possibility is that medicines which are effective in certain patient populations will be developed in preference to those that are effective in other populations. This could be on scientific grounds — for example, because it is easier to develop effective medicines for some racial or ethnic groups than others. Alternatively, it may be on economic grounds — for example, because white Caucasians in developed countries are a wealthier patient group that individuals with the same condition living in developing countries.

There could be implications both for the conduct and design of research, and for the provision of tests and medicines. Will pharmacogenetics increase the likelihood of grouping of patients according to racial or ethnic groups for medical purposes? If so, what might be the ethical and social implications of such an outcome?

Thus, samples cannot be anonymised in the course of research. Some pharmaceutical companies have a policy of not giving individual feedback about genetic information obtained in the course of research because, in the early stages, it may not be possible to provide clinically relevant or useful information to an individual. Such companies, therefore, tend to avoid conducting research in countries where individual feedback is required and anonymous samples are not permitted. Ethics committees which review research often have to consider whether individual feedback is appropriate, and if so, how this process should be managed.

#### Confidentiality, Consent and Decision-making in Primary Care

Will the use of pharmacogenetic tests in primary care raise ethical and legal issues that differ from those raised by other forms of genetic testing? So far, most debate has taken place in the context of genetic testing for disorders, whereas pharmacogenetics is concerned with testing for variation in response to treatment of disorders. Expanding the use of genetic information could have an impact both on individuals and on family members. It may be possible to make some predictions about the response of family members to particular medicines on the basis of information about the tested individual. There could be psychological implications for individuals if pharmacogenetic tests lead them to be classified as 'difficult to treat'. Additionally, the pharmacogenetic information may prove subsequently to have implications for other aspects of an individual's health, such as susceptibility to disease.

Another concern is that individual may find it more difficult to find affordable health insurance as a consequence of a pharmacogenetic test. From the point of view of the insurance industry, individuals may have to pay higher premiums because of their potentially poor response to treatment, regardless of whether or not

they develop the disease for which the treatment would be used. Should providers of health insurance have access to pharmacogenetic information?

There are also implications for providers of healthcare, particularly if patients are concerned about having a pharmacogenetic test. Will patients be able to refuse a pharmacogenetic test if one is available and relevant to their treatment? Will doctors be willing to prescribe medicines for which such tests exist if the patient has not been tested? As we have said, pharmacogenetic tests are unlikely to reveal a definite status of either 'responder' or 'nonresponder' to a particular medicine. Ultimately, who should decide whether or not a patient should take a specific medicine? And if the patient wishes to take the treatment against the advice of the doctor, who should adjudicate?

#### WORKING PARTY ON PHARMACOGENETICS: ETHICAL ISSUES

Questions such as these are posed in the consultation document of the Nuffield Council. Responses to the consultation will inform the deliberations of a Working Party established by the Nuffield Council to consider ethical, legal, social and regulatory issues raised by pharmacogenetics (see Box 2). This group was set up in September 2002 and will meet together over the next 18 months. It comprises a wide range of specialists, including those with experience in

#### Box 2 Terms of reference

- 1 To explore what pharmacogenetics offers now and is likely to offer in the near future.  
In particular to examine the effect of pharmacogenetics on:
  - (a) the design of medicines, the promotion of efficacy and safety in the administration of medicines to individuals;
  - (b) the conduct of trials in the context of pharmaceutical research and development;
  - (c) clinical practice.
- 2 To consider ethical issues specifically raised by pharmacogenetics;  
In particular, to examine the following areas:
  - (a) consent, privacy and confidentiality;
  - (b) the management of information about the likelihood of response to treatment;
  - (c) the implications of differentiating individuals into groups based on the likelihood of response to treatment.
- 3 To consider the implications for the provision of healthcare.

philosophy, genetics, political theory, sociology, primary care, pharmacology and the pharmaceutical industry. As well as the consultation with the public, the Working Party will hold a series of fact-finding meetings with experts in relevant disciplines, including health economists, geneticists, lawyers and representatives of patient groups, regulatory agencies and health insurers. The Council expects to publish the Report of the Working Party in late 2003.

The consultation document can be downloaded from the Council's website: [www.nuffieldbioethics.org/pharmacogenetics](http://www.nuffieldbioethics.org/pharmacogenetics). The closing date for the responses is 19 February, 2003. For further information please contact [bioethics@nuffieldfoundation.org](mailto:bioethics@nuffieldfoundation.org)

#### DUALITY OF INTEREST

None declared.

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- 1 Tollyma P, Guy P *et al.* *A Revolution in R&D*. Boston Consulting Group: Boston, 2001.
- 2 Weber W. *Pharmacogenetics*. Oxford Press: Oxford, 1997.
- 3 See for example Genetic Screening (Nuffield Council on Bioethics, 1993) and Inside Information (Human Genetics Commission, 2002).